

## Review Article

# Efficacy and safety of methylxanthines in the treatment of asthma

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Theophylline is a bronchodilator that also has an anti-inflammatory effect. In Japan, methylxanthines, including theophylline and aminophylline (theophylline ethylenediamine), have been used widely in the treatment of asthma. In some asthma management guidelines, although methylxanthines are recommended for the treatment of asthma, they are not preferred primarily because of potential serious adverse effects in case of overdose. The present review examines the efficacy and adverse effects of sustained-release theophylline and injectable methylxanthines in the treatment of chronic asthma and acute exacerbation of asthma by evaluating reports of published clinical trials and a prospective survey on the occurrence of serious adverse drug reactions to these agents. A prospective survey on the safety of methylxanthines was administered to adult patients (15–64 years of age), mainly with asthma, in medical centers by physicians certified as specialists by the Japanese Society of Allergology. Review of published clinical trials has shown that methylxanthines are effective in controlling asthma. In the prospective study, in the case of sustained-release theophylline, 3921 subjects reported by 66 medical centers and meeting the criteria for inclusion in the survey were selected for analysis. In the case of intravenous methylxanthines, 682 subjects reported by 55 medical centers conforming and meeting the criteria for inclusion in the survey were selected for analysis. None of these subjects exhibited serious adverse drug reaction with sustained-release theophylline or intravenous methylxanthines. In

conclusion, methylxanthines are effective for the treatment of asthma and are safe as long as the dose administered accords with the protocols recommended by asthma management guidelines.

**Key words:** adverse effects, asthma, efficacy, methylxanthines, theophylline.

**INTRODUCTION**

Methylxanthines include theophylline and aminophylline, an ethylenediamine derivative of theophylline, and they have been used widely for the treatment of asthma. Sustained-release theophylline is given orally to control chronic asthma, whereas injectable methylxanthines, including aminophylline and an injectable preparation of theophylline, are given for the treatment of acute exacerbations of asthma. In the past decade, many national and international guidelines for the management of asthma have been published and have recommended the use of theophylline.<sup>1–7</sup> However, some of the guidelines recommend theophylline as an additional bronchodilator for patients with asthma that remains difficult to control after institution of moderate- to high-dose inhaled corticosteroids. Theophylline is not preferred primarily because of possible serious adverse effects that may appear in case of theophylline overdose. Similarly, for acute exacerbation, intravenous aminophylline is recommended for use only in patients who fail to exhibit improvement of severe bronchoconstriction following repeated inhalation of  $\beta_2$ -adrenergic receptor agonists and administration of intravenous corticosteroids and who are admitted to hospital or emergency care, because overdosing with intravenous aminophylline may cause serious adverse effects.<sup>1,3,4</sup>

The *Japanese Guideline for Diagnosis and Treatment of Asthma* published in 1993 by the Japanese Society of

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Allergology (JGL1993),<sup>5</sup> the *Asthma Prevention and Management Guidelines* published in 1998 by a study group supported by the Japanese Ministry of Health and Welfare (JGL1998)<sup>6</sup> and the *Evidence-Based Asthma Management Guidelines* published in 2002 by a study group supported by Ministry of Health and Welfare (EBM-JGL)<sup>7</sup> have all indicated that sustained-release theophylline can be given as an initial drug for mild to severe persistent asthma alone or with low- to high-dose inhaled corticosteroids and/or other anti-asthma agents. These guidelines also note that intravenous methylxanthines can be given in the early stage of moderate to severe acute exacerbation of asthma as the first-line drug with inhaled  $\beta_2$ -adrenergic receptor agonists, subcutaneous epinephrine and/or intravenous corticosteroids.<sup>5–7</sup> The present review examines the efficacy of methylxanthines in the management of chronic asthma and the acute exacerbation of asthma, as well as the adverse effects of this agent. Recent prospective surveys on the safety of methylxanthines in the treatment of asthma will be described.

## EFFECTS OF THEOPHYLLINE

Asthma is characterized clinically by reversible constriction of the airway, induced mainly by spasm of the bronchial smooth muscle, as well as by inflammation of the bronchial wall with infiltration of inflammatory cells, including eosinophils, T cells and mast cells associated with airway hyperresponsiveness and airway remodeling.<sup>8</sup> Theophylline is a bronchodilator that also has extrapulmonary effects, including anti-inflammatory effects. The bronchodilator effect of theophylline may be related to phosphodiesterase inhibition and is observed at high concentrations ( $> 10 \mu\text{g/mL}$  theophylline), whereas the anti-inflammatory effect is observed at lower concentrations ( $5\text{--}10 \mu\text{g/mL}$  theophylline).<sup>9–13</sup>

## EFFICACY AND ADVERSE EFFECTS OF SUSTAINED-RELEASE THEOPHYLLINE IN THE TREATMENT OF CHRONIC ASTHMA IN ADULTS

Clinical trials have shown that sustained-release theophylline is effective in controlling the symptoms of asthma and maintaining pulmonary function. No cases of serious adverse effects have been reported in these clinical trials, although sustained-release theophylline has been reported to produce mild to moderate adverse effects.<sup>9,11,14–18</sup>

The efficacy of sustained-release theophylline was assessed by reviewing the following reports of clinical trials. Clinical trials were subdivided in terms of the type of approach, such as: (i) comparison with inhaled corticosteroids; (ii) comparison of low-dose inhaled corticosteroids plus sustained release theophylline and high-dose inhaled corticosteroids; (iii) add-on effects of sustained release theophylline to high-dose inhaled corticosteroids; and (iv) effects of theophylline withdrawal on asthma symptoms and inflammatory cell regulation.

## Comparison with inhaled corticosteroids

Reed *et al.* compared sustained-release theophylline with inhaled corticosteroid spray as the primary treatment for chronic mild-to-moderate asthma in a double-blind, double-placebo, randomized controlled trial of 1 year duration.<sup>14</sup> They found that both treatments were effective in achieving control of asthma and were accompanied by anticipated adverse effects. Patients with mild-to-moderate asthma received either beclomethasone dipropionate (BDP) spray ( $84 \mu\text{g}$  four times per day) or sustained-release theophylline twice per day in doses adjusted for optimal control of asthma. In this trial, the dose of sustained-release theophylline was adjusted by a blinded study investigator to establish and maintain optimal control of asthma symptoms with minimal adverse effects. To provide guidance and to protect patients from theophylline overdose, an unblinded investigator interpreted theophylline blood levels using a steady state theophylline blood level of  $8\text{--}15 \mu\text{g/mL}$  at approximately 12 h after a dose as the target.

Both sustained-release theophylline and inhaled corticosteroid reduced symptoms promptly and achieved low absenteeism from work or school and low rates of emergency treatment for asthma. Inhaled BDP was slightly but significantly more effective in reducing symptoms and the use of supplementary bronchodilators. With regard to adverse effects, there were no life-threatening adverse reactions attributable to the medications investigated in the study. There were no incidents of seizure, gastrointestinal bleeding or paroxysmal tachycardia. More patients taking theophylline had headaches, insomnia, tremor, nervousness and dizziness, presumably because of its effects on the central nervous system and skeletal muscle, and more also had gastric irritation, dyspepsia, nausea and vomiting. More patients taking BDP had oropharyngeal candidiasis, disturbance of the voice, hoarseness and acute pharyngitis. The mean morning

cortisol levels were similar in the two groups at the beginning of the study, but by 6 and 12 months, cortisol levels were lower in the group treated with BDP inhalation both before and after cosyntropin injection. Review of individual case records disclosed no instance of a morning cortisol level below 5 µg/mL that could be attributed to BDP treatment. This trial showed that sustained-release theophylline effectively controlled symptoms at a steady state theophylline blood level of 8–15 µg/mL without serious adverse effects.<sup>14</sup>

### **Comparison of low-dose inhaled corticosteroids plus sustained-release theophylline and high-dose inhaled corticosteroids**

Evans *et al.*<sup>15</sup> undertook a double-blind, placebo-controlled trial for comparison of low-dose inhaled budesonide (400 µg twice daily) plus theophylline (250/375 mg twice daily) and high-dose inhaled budesonide (800 µg twice daily) for moderate asthma. Both treatments resulted in improvements of pulmonary function that were sustained throughout the study. Treatment with low-dose budesonide plus theophylline resulted in greater improvements of forced expiratory volume in 1 s (FEV<sub>1</sub>). The median concentration of theophylline was 8.7 µg/mL. Concerning adverse effects, both treatments were well tolerated. Nine of 31 patients who received low-dose budesonide plus theophylline reported adverse effects, including gastrointestinal upset, palpitations, sore throat and headache, as did seven of 31 patients who received high-dose budesonide (sore throat, gastrointestinal upset, rosacea and palpitations). No serious adverse effects were reported in this trial. This trial showed that for patients with moderate asthma and persistent symptoms, low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide yielded similar benefits.<sup>15</sup>

Ukena *et al.*<sup>16</sup> undertook a double-blind, placebo-controlled trial for comparison of low-dose inhaled BDP (200 µg twice daily) plus theophylline (250 mg twice daily) and high-dose inhaled BDP (400 µg twice daily) for patients with asthma who were not controlled with BDP 400 µg/day or an equivalent dose of another corticosteroid for 6 weeks. The mean serum theophylline concentration was 10.1 µg/mL in the theophylline group. The FEV<sub>1</sub> and peak expiratory flow (PEF) at week 6 were significantly increased in both groups. There were significant improvements in asthma symptoms and the use of

rescue medication. There were no significant differences in these parameters between the treatment groups. With regard to adverse effects, both treatments were well tolerated. No serious adverse events were reported. Twenty-seven adverse events, which were either pharmacologically predictable or attributable to asthma, were observed in the BDP plus theophylline group (gastrointestinal upset, palpitations and respiratory symptoms, such as dyspnea or cough), whereas 17 events were reported for the BDP 800 µg group (gastrointestinal upset, palpitations and respiratory symptoms). This study demonstrated clinical equivalence of BDP 400 µg/day plus theophylline and BDP 800 µg/day in patients with asthma who were not controlled with BDP 400 µg/day or an equivalent dose of other corticosteroids. The combination of low-dose inhaled steroid plus theophylline is a suitable treatment for moderate asthma.<sup>16</sup>

Lim *et al.*<sup>17</sup> undertook a randomized, double-blind, parallel-group study comparing three treatments in patients with symptomatic asthma who were on 400 µg BDP daily and an inhaled β<sub>2</sub>-adrenergic receptor agonist as required. The treatments examined were as follows: (i) continuing low-dose inhaled corticosteroids alone (BDP 200 µg twice daily); (ii) low-dose inhaled corticosteroids (BDP 200 µg twice daily) and low-dose theophylline (sustained-release theophylline 200 mg twice daily); and (iii) high-dose inhaled corticosteroid (BDP 500 µg twice daily). These medications were given over a 6 month period. There were no overall differences in PEF, diurnal variation or symptom score among the three treatment groups, whereas the greatest within-group improvement in evening PEF was found after the addition of theophylline. No serious adverse effects were reported. There were no significant differences among the treatment groups in any commonly reported adverse effects. In this study, although there was no significant difference among the three treatments in terms of efficacy, the findings suggested that the addition of low-dose theophylline may be beneficial in patients whose asthma is not controlled optimally on low-dose inhaled corticosteroid.<sup>17</sup>

### **Add-on effects of theophylline to high-dose inhaled corticosteroids**

Rivington *et al.*<sup>18</sup> undertook a double-blind, placebo-controlled cross-over study on the effects on pulmonary function of adding sustained-release theophylline (400–600 mg once daily, adjusted to optimal serum concentration), inhaled salbutamol (200 µg four times

per day) and their combination or placebo for 14 days in patients with moderately severe chronic asthma maintained on moderately high doses of inhaled corticosteroids (BDP; mean dose 1100 µg/day). Morning PEF and FEV<sub>1</sub> were significantly higher with sustained-release theophylline alone or with the combination of sustained-release theophylline and salbutamol than with salbutamol alone or placebo. Evening PEF was higher with sustained-release theophylline than with placebo. Evening PEF was higher in the combination group than in the salbutamol alone and placebo groups. No serious adverse effects were reported. Adverse effects reported were mild to moderate in severity and the mean severity ratings for adverse effects reported by patients on the daily diary cards did not differ among treatment groups. This trial demonstrated that the addition of sustained-release theophylline alone or its combination with salbutamol each significantly improved pulmonary function and asthma symptoms in patients treated with high doses of inhaled corticosteroids and as-needed β<sub>2</sub>-adrenergic receptor agonists.<sup>18</sup>

### Effects of theophylline withdrawal on asthma symptoms and inflammatory cell regulation

Kidney *et al.*<sup>11</sup> examined the effect of theophylline withdrawal under placebo control in asthma patients treated with long-term theophylline who were also treated with high-dose inhaled corticosteroids. Theophylline withdrawal was associated with a significant increase in asthma symptoms, particularly at night, and decreases in spirometric measurements and morning PEF. These were accompanied by a significant fall in the number of peripheral blood monocytes (CD14<sup>+</sup>), activated CD4<sup>+</sup> T lymphocytes (CD4<sup>+</sup>/CD25<sup>+</sup>) and activated CD8<sup>+</sup> T cells (CD8<sup>+</sup>/HLA-DR<sup>+</sup>) in patients with plasma theophylline > 5 µg/mL. Bronchial biopsy revealed mirror image findings of those for peripheral blood with increases in CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes in the airway. No serious adverse effects were reported. These observations of theophylline withdrawal suggest that chronic treatment with theophylline, even at low plasma concentrations, controls asthma symptoms, improves pulmonary function and suppresses activated T lymphocyte populations in the blood and decreases the infiltration of these cells in the airway, showing that theophylline has immunoregulatory effects that may be useful in asthma therapy.<sup>11</sup>

Minoguchi *et al.*<sup>9</sup> examined the effect of theophylline withdrawal for 6 weeks in asthmatic patients whose PEF was more than 80% of the predicted value on treatment with both a moderate dose of inhaled dose corticosteroids (BDP; 400–800 µg/day) and low-dose theophylline (400 mg/day) for more than 3 months. Half the patients were withdrawn at random from theophylline. Withdrawal of theophylline caused a significant increase in asthma symptoms, a significant decrease in PEF and a significant increase in the percentage of total and activated eosinophils in the sputum. No adverse effects were described that were attributable to theophylline administration. This trial suggests that long-term treatment with low-dose theophylline has anti-inflammatory effects. The additional use of theophylline with inhaled corticosteroids appears to provide an effective treatment for moderate asthma.<sup>9</sup>

### Summary of the efficacy and adverse effects of sustained-release theophylline

Sustained-release theophylline has been shown to be effective in controlling asthma symptoms and improving pulmonary function. Theophylline, at low doses, is effective for asthma control. Theophylline can be used in patients with milder disease and as an add-on therapy to low to high doses of inhaled corticosteroids when further asthma control is needed.<sup>9,11–18</sup> No serious adverse effects have been reported in these studies. Gastrointestinal symptoms, including nausea, loss of appetite and vomiting, were the most common early events. As long as the target serum concentration was 5–15 µg/mL, as in the studies cited, adverse effects were mild in severity.

### EFFICACY AND ADVERSE EFFECTS OF INTRAVENOUS METHYLXANTHINES ON ACUTE EXACERBATION OF ASTHMA IN ADULTS

Clinical trials have shown that intravenous methylxanthines are effective in controlling the acute exacerbation of asthma. In clinical trials in which serum concentrations were controlled, no cases of serious adverse effects were reported.

The efficacy of intravenous methylxanthines was assessed by reviewing the following reports of clinical trials. Clinical trials were subdivided in terms of the type of approach as follows: (i) effects of intravenous methylxanthines compared with placebo; (ii) dose–response effects of intravenous aminophylline; (iii) decreases in hospital

admission rate by intravenous aminophylline; (iv) less additional treatment of intravenous aminophylline required compared with placebo and add-on effects to inhaled  $\beta_2$ -adrenergic receptor agonist; and (v) a newly developed intravenous theophylline preparation for acute exacerbation of asthma.

### **Add-on effects of intravenous aminophylline to inhaled $\beta_2$ -adrenergic receptor agonists and intravenous corticosteroids compared with placebo**

Montserrat *et al.*<sup>19</sup> treated patients hospitalized because of exacerbation of asthma with intravenous aminophylline or placebo in addition to standard treatment with inhaled salbutamol and intravenous corticosteroids in a randomized, double-blind, placebo-controlled study. In the aminophylline-treated group, the mean ( $\pm$  SD) plasma level of theophylline increased to  $15.2 \pm 3.6$   $\mu\text{g/mL}$  and forced vital capacity (FVC) and FEV<sub>1</sub> increased by  $16 \pm 10$  and  $17 \pm 12\%$ , respectively. The increase in pulmonary functions in the aminophylline-treated group was significantly higher than in the placebo-treated group. No significant changes in arterial oxygen tension or ventilation–perfusion distribution were found, whereas in placebo-treated patients moderate worsening of ventilation–perfusion relationships developed. No adverse drug reactions (ADR) were described for intravenous aminophylline. This trial demonstrated that, when given at therapeutic plasma levels in severe exacerbation of asthma, intravenous aminophylline moderately increased airflow rates without disturbing pulmonary gas exchange.<sup>19</sup>

Huang *et al.*<sup>20</sup> examined the effects of adding intravenous aminophylline to nebulization of albuterol (2.5–5 mg every 0.5–4 h) and intravenous methylprednisolone (60 mg every 6 h) in adults hospitalized for acute exacerbation of asthma in a randomized, placebo-controlled double-blind study. Individualized dose of aminophylline or placebo were given for 48 h. The improvement in FEV<sub>1</sub> at 3 and 48 h of admission in the aminophylline-treated group was greater than in the placebo-treated group ( $P = 0.023$  and  $0.048$ , respectively). The aminophylline-treated group required less nebulization of albuterol. There was no statistically significant difference in adverse effects. This study shows that an individualized dose of intravenous aminophylline added to frequent nebulization of albuterol and intravenous methylprednisolone appears to benefit adults

admitted to hospital with acute exacerbation of asthma and that it is well tolerated when serum concentrations are maintained within the therapeutic range.<sup>20</sup>

### **Dose–response effects of intravenous aminophylline**

Mitenko and Ogilvie<sup>21</sup> examined the physiological responses to intravenously administered aminophylline in nine hospitalized patients with asthma and examined the relationship between pulmonary function and drug administration. Continuous improvement of FVC and FEV<sub>1</sub> was observed over the plasma theophylline concentration range of 5–20  $\mu\text{g/mL}$ . Improvement varied directly with the logarithm of plasma theophylline concentration. With regard to adverse effects, three of nine patients experienced tachycardia with rates of 100–120 b.p.m. at the highest concentration of theophylline (up to 24.6  $\mu\text{g/mL}$ ). Only one of these three patients experienced nausea. Her maximal plasma theophylline concentration was 24.62  $\mu\text{g/mL}$ . No serious adverse effects were reported. In this study, a dose–response relationship was observed for theophylline over the plasma concentration range 5–20  $\mu\text{g/mL}$ . The authors suggested that intravenous theophylline is safe and acceptable for the treatment of asthma within this plasma theophylline concentration range.<sup>21</sup>

### **Decreases in hospital admission rate by intravenous aminophylline**

Wrenn *et al.*<sup>22</sup> undertook a randomized, double-blind, placebo-controlled intervention study to assess the role of aminophylline in the treatment of acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD) when used in addition to the inhaled  $\beta_2$ -adrenergic receptor agonist metaproterenol and intravenous methylprednisolone. There was a threefold decrease in hospital admission rate for patients treated with aminophylline (6%) compared with those who received placebo (21%;  $P = 0.016$ ). Concerning adverse effects, there was no difference in the frequency of adverse effects, except for a trend towards a higher frequency of nausea in the aminophylline group. This trial suggested that aminophylline at a dose just below the commonly accepted therapeutic range appeared to decrease the rate of hospital admission of patients with exacerbation of asthma or COPD.<sup>22</sup>

### **Less additional treatment with intravenous aminophylline required compared with placebo and add-on effects to inhaled $\beta_2$ -adrenergic receptor agonists**

Ohta *et al.*<sup>23</sup> treated acute exacerbation of asthma with intravenous aminophylline or inhaled salbutamol as the initial treatment for the first hour. In the aminophylline-treated group, the dose of aminophylline was designed to yield a serum concentration of theophylline between 15 and 20  $\mu\text{g/mL}$  within the first hour. The salbutamol-treated group received four puffs (400  $\mu\text{g}$  salbutamol) delivered via a metered-dose inhaler every 15 min for the first hour. One hour after initiation of treatment, the effectiveness of the treatment was assessed. If the initial treatment did not relieve exacerbation of asthma within the first hour, the opposite treatment regimen was administered additionally. Most patients seen in the emergency clinic had already received inhaled short-acting  $\beta_2$ -adrenergic receptor agonists in both the aminophylline and salbutamol treatment groups. Only six of 34 patients (18%) who received intravenous aminophylline first needed additional treatment with inhaled salbutamol 1 h after initiation of treatment to control exacerbation of asthma, whereas 17 of 19 patients in the salbutamol group (89%) needed additional treatment with intravenous aminophylline. Intravenous aminophylline exhibited add-on effects to repeated inhalation of salbutamol. Concerning adverse effects, no adverse reactions were reported in either group. This study showed that intravenous aminophylline could be as beneficial as salbutamol given by metered-dose inhaler for acute exacerbation of asthma.<sup>23</sup>

### **A newly developed intravenous theophylline preparation for the treatment of acute exacerbation of asthma**

Inoue *et al.*<sup>24</sup> examined the effects of a newly developed intravenous theophylline preparation in 16 asthmatic patients with mild acute exacerbation. They administered 200 mg theophylline with 200 mL saline over 2 h. After intravenous theophylline, PEF and  $\text{FEV}_1$  increased significantly and asthma symptoms improved significantly. As for adverse effects, none of the recipients had any adverse effects. This trial showed that the newly developed intravenous theophylline preparation was effective in controlling the acute exacerbation of asthma and exhibited no adverse effects.<sup>24</sup>

### **Summary of the efficacy and adverse effects of intravenous methylxanthines**

The studies described above and other controlled clinical studies have shown that intravenous aminophylline/theophylline has bronchodilator effects and is effective for the treatment of exacerbation of asthma.<sup>19–31</sup> In the EBM-JGL, 22 studies were cited as scientifically valuable in determining the clinical usefulness of intravenous aminophylline.<sup>7</sup> In all studies except one, the loading dose was 5.6–6.0 mg/kg bodyweight and the maintenance dose was 0.6–0.9 mg/kg bodyweight. Fifteen of 22 studies found that aminophylline alone was effective in improving acute exacerbation of asthma. Seven studies found that intravenous aminophylline was effective in combination with other agents. Two studies reported that intravenous aminophylline did not exhibit add-on effects to treatments given beforehand.<sup>32,33</sup> Three studies did not support the use of intravenous aminophylline because it did not improve asthma exacerbation and adverse effects, such as headache, were frequent.<sup>34</sup> In randomized clinical studies, aminophylline exhibited add-on effects to salbutamol or epinephrine.<sup>22,24,25</sup> One double-blind study showed that intravenous aminophylline decreased the percentage of hospital admissions compared with placebo (6 vs 21%).<sup>22</sup> In one study of pregnant patients who were kept on high doses of corticosteroids, intravenous aminophylline did not shorten hospital admission.<sup>34</sup>

No serious adverse effects of intravenous aminophylline administered for the treatment of acute exacerbation of asthma were reported in the studies cited in the present review. In most studies, there were no differences in less serious adverse effects between intravenous aminophylline and controls, although nausea appeared to be more frequent in aminophylline-treated groups.

Together, these findings indicate that intravenous aminophylline and theophylline are effective in treating asthma exacerbation and are safe as long as the doses used are within the therapeutic range.

### **PROSPECTIVE SURVEY OF THE SAFETY OF METHYLXANTHINES IN THE LONG-TERM CONTROL OF ASTHMA AND TREATMENT OF ACUTE EXACERBATION<sup>35,36</sup>**

In Japan, methylxanthines have been used widely for the long-term control of chronic asthma and also for the treatment of acute attacks of asthma, as recommended

in the *Asthma Prevention and Management Guidelines*.<sup>5-7,37</sup> In contrast, some international guidelines and national guidelines of other countries recommend the use of sustained-release theophylline for chronic asthma and also recommend intravenous aminophylline for the treatment of severe exacerbation of asthma, but these drugs were recommended as an alternative therapy or not preferred principally because of potential serious ADR.<sup>1,2,4</sup>

With this background, a subcommittee of the Asthma Prevention and Management Guideline Committee in Japanese Society of Allergology (JSA) conducted a survey of the safety of theophylline and aminophylline products in the treatment of asthma and COPD.<sup>35,36</sup>

The purpose of this survey was to search for serious ADR to sustained-release theophylline and intravenous methylxanthines (theophylline and aminophylline) in adult patients (15–64 years of age) with asthma or COPD. Serious ADR was defined as any untoward medical occurrence that, at any dose: (i) results in death or is life threatening; (ii) requires hospitalization or prolongation of hospitalization; (iii) results in persistent or significant disability/incapacity; (iv) results in a congenital anomaly/birth defect; and (v) does not meet any of the above criteria for serious ADR, but may jeopardize patients/subjects or may require medical or surgical intervention to prevent one of the outcomes listed above.

In medical centers with physicians certified as specialists by the JSA, patients were registered to survey for a arbitrary 1 month period between 1 September and 31 December 2001. In the case of use of sustained-release theophylline, investigations were performed for 1 month after registration and in the case of the use of intravenous methylxanthines, investigations were performed during the infusion and for 6 h after infusion.

The following items were investigated in the survey: sex/age, date of registration, reason for administration (diagnosis), route of administration, dose and term of administration, drugs administered other than methylxanthines and ADR and their severity.

For sustained-release theophylline, 3921 subjects were selected for analysis among 4983 subjects reported by 66 medical centers meeting the criteria for inclusion in the survey. Of the subjects, 93.3% were patients with asthma, 5.2% were patients with COPD and 1.5% were patients with both asthma and COPD. For intravenous methylxanthines, 682 subjects were selected for analysis among 876 subjects reported by 55 medical centers meeting the criteria for inclusion in the survey. Of these

subjects, 98.7% had asthma and the remaining patients had COPD.

### **Doses of sustained-release theophylline and intravenous methylxanthines**

Sustained-release theophylline 300–400 mg/day was administered to 61.5% of patients. Of 610 subjects who received intravenous aminophylline, 41.0% received 125 mg/day aminophylline and 43.2% received 250 mg/day aminophylline. Of 77 subjects who received intravenous theophylline, 88.3% received 200 mg/day theophylline.

### **Occurrence of serious ADR**

No serious ADR were observed, not only in subjects selected for analysis, but also in subjects not selected for analysis because they did not meet the inclusion criteria.

### **Occurrence of non-serious ADR**

With sustained-release theophylline, non-serious ADR were observed in 54 of 3909 subjects (1.38%), including tremor, insomnia, hypertonia, nausea, dyspepsia, abdominal distension and palpitations. With intravenous methylxanthines, non-serious ADR were observed in two of 682 subjects (0.29%), including palpitations, nausea, vomiting, tachycardia, flushing, headache, tinnitus and perspiration. With sustained-release theophylline, the incidence of ADR was not significantly related to the dose of the drug administered during the survey period and diseases for which the drug was used. Neither age nor sex was related to the incidence of ADR. Among the patients receiving sustained-release theophylline, the incidence of ADR was high for those with no previous treatment with sustained-release theophylline. The incidence of ADR was high for patients who received concomitant therapy with macrolides, but was not related to the use of corticosteroids and  $\beta_2$ -adrenergic receptor agonists.

### **Conclusions**

Methylxanthines, including theophylline and aminophylline, are safe agents for the treatment of asthma and COPD as long as they are used properly.

## EFFICACY AND ADVERSE EFFECTS OF SUSTAINED-RELEASE THEOPHYLLINE IN THE TREATMENT OF CHILDHOOD ASTHMA

In Japanese guidelines, sustained-release theophylline is recommended for the control of persistent childhood asthma and can be given alone or in combination with other controllers, although in GINA 2002 the role of methylxanthines in long-term treatment in childhood asthma is limited.<sup>2,6,7,38</sup> Because the anti-asthma effects of theophylline can be detected even at a concentration of 5 µg/mL and adverse effects are observed more frequently at concentrations above 20 µg/mL, the recommended therapeutic concentration range for theophylline is 5–15 µg/mL.<sup>2,7,38,39</sup>

Three randomized clinical trials on sustained-release theophylline will be discussed from 15 reports cited in the section regarding childhood asthma in the EMB-JGL.<sup>7</sup>

As a comparison of effects of sustained-release theophylline to those of oral  $\beta_2$ -adrenergic receptor agonists in childhood asthma, Nishima *et al.* undertook a randomized, double-blind, placebo-controlled study on childhood asthma patients (6–12 years of age) comparing sustained-release theophylline (200–600 mg/day) and trimetoquinol (1–3 mg/day).<sup>40</sup> Sustained-release theophylline yielded significantly higher improvement of asthma symptoms and pulmonary functions than the oral  $\beta_2$ -adrenergic receptor agonists. No serious adverse effects were reported in either group. Milder adverse effects were more frequent in the sustained-release theophylline group. This study showed that sustained-release theophylline was effective for chronic childhood asthma and without serious adverse effects.<sup>40</sup>

As a comparison of the effects of sustained-release theophylline with those of inhaled disodium cromoglycate in childhood asthma, Hambleton *et al.*<sup>41</sup> performed a randomized, double-blind, placebo-controlled cross-over study of patients with childhood asthma (6–16 years of age) using sustained-release theophylline, cromoglycate and their combination. No significant difference in pulmonary function was noted among the three treatment groups. The percentage of symptom-free days was higher in the theophylline and combination groups than in the cromoglycate group. No serious adverse effects were reported in any of the three treatment groups. The incidence of adverse effects did not differ between the three treatment groups. This study showed that sustained-release theophylline was effective in the treatment of

chronic childhood asthma without any serious adverse effects.<sup>41</sup>

As a comparison of sustained-release theophylline with inhaled corticosteroids in children with asthma, Tinkelman *et al.*<sup>42</sup> undertook a double-blind, placebo-controlled trial for the comparison of inhaled BDP (84 µg four times a day) and sustained-release theophylline administered twice daily in doses adjusted for optimal control of symptoms in children aged between 6 and 16 years with mild-to-moderate asthma. Both aerosolized BDP and sustained-release theophylline were effective primary treatments for mild-to-moderate chronic asthma in children. There were no life-threatening adverse events attributable to study medications reported. There were no spontaneous reports of seizures, coma, gastrointestinal bleeding or paroxysmal tachycardia. Other adverse effects were observed significantly more frequently with theophylline than with BDP. Growth velocity suppression was noted with BDP. This study shows that both theophylline and BDP are effective for the treatment of mild-to-moderate asthma in children. The dose of sustained-release theophylline should be determined following recommended protocols and repeated measurement of serum levels of theophylline is recommended.<sup>42</sup>

## Summary of the efficacy and adverse effects of sustained-release theophylline in childhood asthma

Sustained-release theophylline alone or in combination with other anti-asthma agents is recommended for the treatment of children with mild-to-severe persistent asthma. The dose of theophylline should be determined following recommended protocols and repeated measurement of serum levels of theophylline is recommended, because there may be serious adverse effects with overdosing.<sup>1,2,6,7</sup>

## EFFICACY AND ADVERSE EFFECTS OF INTRAVENOUS METHYLXANTHINES IN THE TREATMENT OF ACUTE EXACERBATION IN CHILDHOOD ASTHMA

According to asthma management guidelines of Japan, intravenous methylxanthines can be given as bolus injections or drip infusions to treat acute exacerbation of asthma that is greater than of moderate severity.<sup>6,7,38</sup> In contrast, in the section of hospital-based management of exacerbation of childhood asthma in GINA 2002,<sup>2</sup>



intravenous methylxanthines are recommended for consideration only as an alternative therapy for the treatment of acute exacerbation of asthma because of their increased numbers of adverse effects. Moreover, there are reports that intravenous aminophylline does not exhibit add-on effects in children with severe asthma who are already being treated with inhaled  $\beta_2$ -adrenergic receptor agonists and intravenous corticosteroids.<sup>43,44</sup> No serious adverse effects have been reported in studies in which serum levels were controlled within the recommended range. A high level of serum theophylline was associated with neurological or cardiovascular adverse effects.<sup>45</sup> Because the metabolism of methylxanthines varies widely in children depending on age, medications and the presence of fever and/or viral infection, the dose of intravenous methylxanthines should be determined following recommended protocols and repeated measurement of serum levels of theophylline is recommended.<sup>2,38</sup>

### Summary of the efficacy and safety of intravenous aminophylline in the treatment of acute exacerbation in childhood asthma

Taken together, the available information indicates that intravenous methylxanthines can be given as bolus injections or drip infusions to treat acute exacerbation of childhood asthma of more than moderate severity. Intravenous methylxanthines are safe as long as their dose is determined following recommended protocols. Repeated measurement of serum levels of theophylline is recommended.

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